

Lund 1980

BIOCHEMICAL CHANGES IN HOSPITALIZED CHRONIC MALE ALCOHOLICS

by

JAN WADSTEIN
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1980
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Biochemical Changes in Hospitalized Chronic Male Alcoholics

AKADEMISK AVHANDLING

som med vederbörligt tillstånd av Medicinska Fakulteten vid Lunds Universitet för avläggande av medicine doktorsexamen kommer att offentligen försvaras i Universitetsklinikernas aula Malmö allmänna sjukhus, lördagen den 17 maj, 1980, kl 09.15 (precis).

av

Jan Wadstein
med lic (ld)

Malmö 1980

ABSTRACT

Lund University

Doctoral Dissertation
Date of issue, May 17, 1980
Codon: LUMEDV/(MEMA-1003)/
1-55/1980

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Biochemical changes in hospitalized chronic male alcoholics.

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S-GT as well as S-ASAT are elevated in 69 and 73 per cent respectively at admission to hospital. S-ALAT is elevated in 53 per cent. During abstinence there is a decrease in these "hepatic enzymes" with a normalization of S-ASAT and S-ALAT for those patients with only moderately elevated values. The GT decrease is slower and after 9 days there remains an elevation in most of the patients. One factor affecting the elevation of the hepatic enzymes could be length of debauch. Patients with a long history of alcoholism achieve the highest levels of ethanol, but also have the shortest length of debauch.

HDL is changes in the subclasses in all the 8 investigated patients. HDL seems in combination with the other parameters to be valuable in detecting alcoholism.

The pancreas is affected in patients with long history of alcoholism which is demonstrated both by help of isoamylase studies and ERCP. In patients with more than 5 years of alcoholism there is a high incidence of both morphological changes in the pancreas and pathological isoamylase pattern.

S-potassium seems to decrease just before and during delirium tremens. After the DT episode there is a rapid normalization of S-potassium. S-potassium seems to be a good predictor and a helpful aid in differential diagnoses in patients with possible delirium tremens.

Key words: Alcoholism, aspartate aminotransferase, alanine aminotransferase, bilirubin, gamma-glutamyltransferase, lipoprotein, zonal ultracentrifugation, pancreatitis, ERCP, delirium tremens, hypokalemia.

Language: English,

Pages: 1-55

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Alcohol Diseases Malmö General Hospital Malmö Sweden**

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This thesis is based on the following papers which will be referred to in the text by their Roman numerals:

- I. G Skude & J Wadstein: Amylase, Hepatic Enzymes and Bilirubin in Serum of Chronic Alcoholics. Acta Med. Scand. 201: 53-58 1977.
- II. J Wadstein & G Skude: Changes in Amylase, Hepatic Enzymes and Bilirubin in Serum upon Initiation of Alcohol Abstinence. Acta Med. Scand. 205:313-316, 1979.
- III. J Wadstein & G Skude: Serum Ethanol, Hepatic Enzymes and Length of Debauch in Chronic Alcoholics. Acta Med. Scand. 205:317-318, 1979.
- IV. B Danielsson, R Ekman, G Fex, B G Johansson, H Kristenson, P Nilsson-Ehle & J Wadstein: Changes in Plasma High Density Lipoproteins in Chronic Male Alcoholics during and after Abuse. Scand. J. Clin. Lab. Invest. 38:113-119, 1978
- V. J Ariyama, G Skude, J Wadstein & L Wehlin: Alcoholic Pancreatitis in Sweden, Stomach and Intestine vol 9, 12: 1575-1583, 1974.
- VI. J. Wadstein & G. Skude: Does Hypokalaemia Precede Delirium Tremens? Lancet 9:549-550, 1978



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Abbreviations

S-ASAT	Serum aspartate aminotransferase (GOT)
S-ALAT	Serum alanine aminotransferase (GPT)
S-GT	Serum gammaglutamyltransferase
P-HDL	Plasma high density lipoproteins
VLDL	Very low density lipoproteins
ERCP	Endoscopic retrograde pancreatography
DT	Delirium Tremens
S	Serum
P	Plasma
U	Urine

Introduction

The frequency of alcoholism is increasing in Sweden. It is now obvious that about 10 per cent of the adult male population are heavy consumers of alcohol with increased alcohol tolerance. (1) It is also a well-known fact that alcohol causes many serious illnesses requiring hospital care. On the other hand many patients hospitalized for other reasons are chronic alcoholics or have excessive drinking habits. Jarman and Kellett (2) reported drinking problems in 25 per cent of hospital admissions in England. This prevalence was sixfold greater than that recorded in a community survey using the same technique, where drinkers tended to be male, heavy smokers and younger than non drinkers. One of the largest studies made in this field was done by Roch (3) who in Switzerland found that among 2.075 male in-patients at medical and surgical clinics in 1939 about 8.2 per cent had a history of alcoholism. The rates reported by different authors vary between 20-48 per cent of medical and/or surgical in-patients. (4-10)

The degree of alcoholism is difficult to compare in different studies because of variations in definition and the large spectrum of somatic manifestation of alcohol damage. The aim of the present investigation which started in 1973, is to elucidate some biochemical markers in chronic male alcoholics. Special interest is focused on the following problems: 1) The response of biochemical markers to chronic alcoholism, 2) the decrease of values of biochemical markers during abstinence, 3) the influence of ethanol levels in serum on these biochemical markers, especially S-GT, and 4) the interrelationships between the different biochemical markers. By using several different tests it is possible to accurately detect chronic alcoholism. All of these tests, aside from ethanol in serum, are, however, nonspecific and causes other than alcohol must be considered.

Study population

The studies presented include a total of 396 male patients voluntarily hospitalized at the clinic for Alcohol Diseases during 1973-77. All patients fulfilled the well-known criteria for chronic alcoholism defined by Jellinek. (11, 12) The patients also satisfy the requirements of Kaij (13) in accordance with Goodwin (14) who include restorer, black-outs and uncontrolled drinking. Acceptans criteria are described more exactly in the description of each study. Special interest is focused on the duration of alcoholism and the length of the current debauch. The pattern of alcohol consumption often varies from time to time in the same individual and the genetic

resistence toward alcohol varies in a population.

In this work the following parameters are discussed as biochemical markers of alcoholism:

S-Bilirubin (I, II, III)

S-ASAT (I, II, III, V)

S-ALAT (I, II, III)

S-GT (I, II, III, IV)

S-Ethanol (II)

P-HDL (IV)

S-Pancreas isoamylase (I,II, V)

S-Potassium (VI)

S-Bilirubin, S-ASAT, S-ALAT and S-GT (I, II, III)

In paper I the study population consists of 182 male in-patients aged 25 to 72 years at the Clinic of Alcohol Diseases, Malmö General Hospital, Malmö Sweden. The patients had been hospitalized for detoxification, and social or psychiatric rehabilitation in connection with an acute ethanol intoxication. All patients fulfilled the above described criteria for chronic alcoholism. All patients except 3 were registered with the Temperance Board. 48 of the patients had had at least one episode of delirium tremens, but not during the present admission. None had verified cirrhosis of the liver. 17 had suffered one or more attacks of acute pancreatitis. All patients were voluntarily admitted for treatment of alcoholism at this clinic. The reference group for normal values comprised at least 97 male shipyard workers, age 19-63 years. The history of drinking habits in the reference group was not obtained. They were assumed to be representative for Swedish factory workers.

Blood samples were obtained from the patient group on admission and analyzed for Serum-Bilirubin, serum-ASAT, serum-ALAT and S-GT. The samples from both groups were analyzed within 20 hours after collection. Bilirubin was determined in a Technicon Auto Analyzer with a modification of the method by Jendrassik And Grof (15). The serum activities of ASAT and ALAT were determined with an LKB Reaction Rate Analyzer 8.600 at 37°C using reagents from

Kabi, Stockholm, Sweden; the results are given in U/l (37°) and $\mu\text{kat/l}$ (37°). GT activity was determined with γ -glutamyl-P-nitroanilide as substrate according to Orłowski and Meister. (16)

The patients were divided into groups according to the duration of alcoholism with a period of 0-5, 5-10, 10-20 and more than 20 years after fulfillment of the criteria for chronic alcoholism.

In paper II blood samples from 156 male in-patients were analyzed for the same hepatic enzymes as in paper I and serum levels were followed during the following 9 days. The analyse methods are the same as above. Serum albumin was determined in a Technicon Auto Analyzer with Bromcresol Green.

Résults

S-Bilirubin

S-bilirubin was determined in 338 patients. The bilirubin values gave identical arithmetic means in both the reference group and the groups of chronic alcoholics, but S.D. was significantly higher in all groups of alcoholics than in the reference group ($p < 0.05$). In all groups there were single pathologically elevated values most frequently in the duration groups of 0-5 and 10-20 years. The overall frequency of pathologically elevated values among the alcoholics was 12 per cent and 3 per cent in the reference group.

S-ASAT

In all duration groups among the 338 patients in paper I and II were mean values of S-ASAT significantly increased compared to the reference group (p in all cases being $< 0,001$). 73 per cent had values exceeding the upper normal limit for S-ASAT (paper I). The highest activities were found in the duration group 10-20 years. With longer alcoholism the mean was somewhat lower. The range among the alcoholics was very wide from the lower normal limit to about 15 $\mu\text{kat/l}$ (900 U/l). A decrease in activities of S-ASAT was seen during the observation time in all groups among the 156 patients in paper II. However, only patients with moderate initial increase showed a complete normalization. 36 per cent of the patients still had a pathologically elevated S-ASAT activity after 9 days of ethanol abstinence.

S-ALAT

S-ALAT was determined in the 338 patients described above. The mean values of S-ALAT were significantly increased in all duration groups ($P < 0,001$), but with slighter elevation than for S-ASAT (paper I) 53 per cent of the patients had increased activities of S-ALAT (paper I). The highest activities were found in duration group 10-20 years with a wide range of variation as for S-ASAT. The decrease of S-ALAT in the second study follows the pattern for S-ASAT.

S-GT

S-GT was determined in the same study populations described above. Of the alcoholics 69 per cent had elevated S-GT activity (paper I), the mean serum activities being significantly higher in all groups than in the reference group ($p < 0,001$). The highest value was found in duration group 5-10 years, i.e. somewhat earlier than for S-ASAT and S-ALAT. Longstanding alcoholism showed a tendency toward normalization of S-GT activities. The mean value in the group with more than 20 years of alcoholism being significantly lower than in duration group 5-10 years. ($p < 0,01$). The range was wide with values from normal to 59 $\mu\text{kat/l}$ (3.500 U/l).

The decrease in S-GT occurs very slowly during abstinence. Only in the group with activities greater than 5 times the upper normal limit was a rapid decrease seen. Of all patients, 74 per cent, had an increase S-GT activity after 9 days of abstinence.(paper II)

Correlation of enzymes to serum ethanol concentration

In the third study serum concentrations of ethanol, S-ASAT, and S-GT were determined in 40 male chronic alcoholics at admission to hospital. The analyses of S-ASAT and S-GT were done in the same way as described above and serum ethanol concentration was determined by gas chromatography. The alcoholics were divided into groups according to the duration of alcoholism: 0-5, 5-10, and more than 10 (mean 18) years and of the current debauch.

Results

The mean S-GT activity was in the reference range when the debauch period was shorter than 2 weeks, slightly elevated with a debauch of 2-6 weeks, and markedly increased when the drinking period exceeded 6 weeks independent of the duration of chronic alcoholism.

S-Ethanol in serum increases with duration of alcoholism. S-GT mean values are correlated to length of debauch. The mean duration of debauch was shortest in cases with long-standing alcoholism.

Pancreatic-serum-isoamylase (I, II, IV)

Samples for determination of pancreatic isoamylase activity were obtained from a total of 356 alcoholic patients. Determination of serum amylase activity was performed with Phadebas Amylase Test (Pharmacia, Upsala, Sweden) and agarose gel electrophoresis was used to separate and detect the salivary and pancreatic isoamylase of serum (20). The relative contributions from each isoenzyme were determined by densitometric scanning.

Results

No difference in means of total serum amylase activity was seen between duration groups (182 patients). There was a slightly larger range of values in group 5-10 compared with the control group ($p = 0.05$). The mean for pancreatic isoamylases of serum was decreased in the groups with long-standing alcoholism compared with the reference group, $p = 0.05$ for duration group 10-20 and < 0.05 for duration group more than 20 years. The frequency of subnormal serum activity of the pancreatic amylase was 2 per cent in the reference group, 12 per cent in alcoholics in duration group 0-5, 19 per cent in group 5-10, 23 per cent in group 10-20 and 26 per cent in the duration group more than 20 years.

The frequency of abnormally high activities of the pancreatic isoamylase in serum was not increased among alcoholics compared to controls. The progressive change seen above was not seen in frequencies of elevated pancreas isoamylase among duration groups. In all groups the S.D. was greater than in the reference group ($p < 0.001$). During the abstinence period a decrease of initially elevated values was seen. However, patients whose initial pancreatic serum amylase was low or normal, showed an increase during the abstinence period at the end of which 34 per cent had a pathologically increased activity and only 5 per cent a decreased activity. No correlation was found between pancreatic isoamylase activity and the activities of S-ASAT or S-GT. Simultaneous determinations of albumin in the 5 groups give means of 43, 43, 45, 43 and 44 g/l.

S-HDL (V)

HDL levels were studied in 38 male chronic alcoholics 25 to 59 years of age. All were intoxicated at admission to hospital with plasma ethanol concentrations between 24 and 62 mmol/l. Their last debauch had lasted for more than 4 weeks. The patients' diet before admission to hospital was not controlled. 12 apparently healthy men aged 48 years served as controls. All blood samples were kept at 4°C and analyzed within 48 hours. Monospecific antisera against HDL och LDL were available at the Dept. of Clinical Chemistry. HDL protein was determined by electroimmuno assay (17) and the results were expressed as per cent of the value of pooled plasma from healthy subjects. Serial samples from 8 patients were subjected to separation of HDL into subfractions using zonal ultra centrifugation and following the procedure described by Danielson et al (18). Ethanol was determined fluorometrically (19). S-ALAT, S-ASAT, and S-GT activities were determined as mentioned above.

Results

Table 1, paper V describes the increased values of S-GT, HDL, HDL-cholesterol and a combination of parameters. In the 8 patients undergoing further studies of the composition of the increased HDL lipoprotein fraction, all patients showed abnormal distribution patterns of HDL subclasses. 5 patients showed a moderate increase of a somewhat broad asymmetrical HDL III fraction with a shoulder of relatively small HDL II component. In the other 3 patients a 4-5 fold increase of symmetrical distributed HDL II fraction was seen as the main alteration. Qualitative alterations in HDL were normalized in parallel to HDL cholesterol and lipoprotein during a period of one week.

Changes in Serum Potassium as a Predictor of Delirium Tremens (VI)

Development of delirium tremens was anticipated in 37 chronic alcoholics admitted to hospital for detoxification. Suspicion was based on history as well as duration and intensity of the interrupted alcohol debauch. None of the patients had a manifest diabetes mellitus or known liver cirrhosis. Delirium tremens developed in 26 of the 37 patients (DT group).

Results

In the DT group there was a rapid fall in serum potassium to subnormal values which preceded the DT. After the DT episode the S-potassium increased slowly to normal values. There were no significant changes in urine potassium in the 6 DT patients whose urine samples were analyzed. Serum concentrations of sodium, magnesium, creatinine and sodium bicarbonate were normal in all patients. PO_2 , PCO_2 , pH and base excess did not change significantly in the 6 DT patients in whom these variables were studied in arterial blood.

Serum-pancreas-isoamylase activity and ERCP (V)

18 of the chronic alcoholics with clinical suspicion of pancreatic disease were studied. S-isoamylase activity was determined as described (20). The fiberduodenoscopes, Olympus JF-B and JF-B2 were used. Urografin was used for visualization of the pancreatic duct. Diagnostic criteria of pancreatogram for pancreatitis are shown in table 2 paper V. Pancreatitis was termed minimal, moderate or severe according to the degree of pancreatographic abnormalities.

Results

Among the 18 cases selected for ERCP, pancreatogram was abnormal in 12 cases (66.7 per cent). S-pancreas isoamylase levels in the 18 cases were low in 7 cases (38.9 per cent), high in 2 cases (11.1 per cent) and normal in 9 cases (50 per cent). One case of low amylase and normal pancreatogram and 4 cases of normal amylase and pathological pancreatogram were seen, indicating 27 per cent (5/18) discrepancy between the two tests in this study material. The pancreatogram in 15 cases with a history of alcoholism more than 5 years and with delirium tremens was normal in 4 cases (26.7 per cent) and abnormal in 11 cases (73.3 per cent). On the other hand 11 of 12 cases with abnormal pancreatogram (91.7 per cent) had a history of alcoholism of more than 5 years duration. 6 patients (43.3 per cent) showed a sign of pancreatic calcification and 9 patients (50 per cent) of chronic relapsing pancreatitis.

General discussion

The identification of an alcoholic is obviously very important at hospital as well as in ambulatory praxis. Many cases are missed because of lack of knowledge about alcohol dependent diseases. New causal relationships between alcohol and many somatic conditions are revealed every year. The biochemical analyses of "hepatic enzymes", bilirubin, HDL and pancreatic iso-amyase could be a helpful aid in the detection of alcoholism.

Concerning bilirubin in serum, hyperbilirubinemia in chronic alcoholics has been reported earlier. (21, 23) In this investigation we found no significant difference from the reference group, but a few or single pathologically high values were seen in our groups. These individuals always had pathological values of at least 1 of the enzyme tests used to indicate hepatic cellular damage. Bilirubin as a tool to detect chronic alcoholists and alcoholism is of little value. The other tests seem to be more sensitive and bilirubin is useful only as a complement to the other enzyme analyses. When bilirubin is elevated in combination with high serum enzymes, among these patients, it is nearly always a sign of cholestasis in alcohol hepatitis, fibrosis or cirrhosis. (23)

S-ASAT was elevated in 73 per cent of 182 patients which is in agreement with other authors. (21, 24, 25). Solitary S-ASAT elevation is sometimes found as the only sign of alcoholism. This elevation could be due to hepatic damage but also to a liberation of S-ASAT to serum from other tissues, such as skeletal muscle and myocardium. Cholelithiasis must also be considered (31). The decrease in S-ASAT occurs slowly and only those values slightly above the upper normal limit are normalized during an observation time of 9 days. For those values which remain elevated 9 days after withdrawal of alcohol, the initial activity may be assumed to have been more than twice the upper normal limit.

S-ALAT appears to be less sensitive than S-ASAT or S-GT in detection of alcoholism. Isolated S-ALAT elevation was not seen in any of the 338 patients observed. In the first paper (182 patients) S-ALAT was elevated in 53 per cent of alcoholics at admission to hospital. S-ALAT gives no more certain information about the patients' alcoholism than S-ASAT or S-GT, but may indicate hepatic steatosis. There is a high correlation between

S-ASAT and S-ALAT, $r=0.84$.

S-GT is often assumed to be one of the most sensitive test for alcoholism (24, 25, 32, 37). In the first paper S-GT was elevated in 69 per cent of 182 alcoholics with the highest mean in the duration group of 5-10 years. This is somewhat earlier than for S-ASAT and S-ALAT. In longstanding alcoholism there is a tendency toward normalization of S-GT activities. This tendency is difficult to explain. It may reflect a genetic selection of individuals with somatic resistance to ethanol in the group that has survived more than 20 years as chronic alcoholics. It may also indicate reduced enzyme synthesis in a diseased liver with reduced functioning cell mass. Such factors as length of debauch and current ethanol consumption may also influence S-GT levels. The level of S-GT is not normalized after 9 days of observation, even in patients with moderately elevated values. Thus it can be concluded that determination of S-GT, within 9 days after alcohol withdrawal may be used as a measure of previous heavy alcohol consumption. Using the combination of S-ASAT and S-GT, 8 per cent of the patients in paper I showed normal activity even though they were severe alcoholics. The high frequency of elevated S-ASAT and S-GT values and the rather slow decreases in these levels among alcoholics make them especially valuable in both detection and following patients with alcohol overconsumption. The presence of false negative values should, however, not be overlooked in screening procedures. False positive elevations must also be considered (38-40).

Elevated concentration of HDL in alcoholism have been reported (34, 42). In paper IV elevated concentration of HDL were seen in 65 per cent of the total material consisting of 38 chronic alcoholics. Elevated levels of HDL cholesterol were found in a comparable percentage. The reason for increased HDL concentration in alcoholics is unknown, but a closer characterization of the HDL fraction reveals a selective increase in the HDL II subfraction, whereas the HDL III fraction is generally normal. The lipoprotein pattern in chronic alcoholism may be explained by an increased turnover of VLDL and a parallell increase in HDL concentration. Lipoprotein

lipase activities are significantly higher in alcoholics than in normals (43, 44). After cessation of ethanol intake all lipoprotein fractions normalized within 1-2 weeks and the decrease of HDL II concentrations is dramatic. The time course of this normalization closely parallels the decrease of lipoprotein lipase activities to normal levels. Although there are many questions about the course of lipid changes in alcoholism the determination of HDL could be useful in detection of chronic alcoholism. In combination with S-GT one could possibly detect 95 per cent of the alcoholics (table II paper IV), after debauch.

The effects of ethanol on the pancreas were first described at the end of 19th century (45, 46). It is not known how the effects are mediated on the cellular level. A relationship between alcohol consumption pattern and acute (47, 48) and chronic (49-51) pancreatitis has earlier been described. Subnormal levels of pancreatic amylase were found in 2 per cent of the reference group, 12 per cent of the alcoholics in duration group 0-5 years, 19 per cent in group 5-10, 23 per cent in group 10-20 and 26 per cent in the duration group with more than 20 years of alcoholism. This indicates a decrease in exocrine pancreatic function, i.e. increased prevalence of alcoholism in agreement with earlier studies (47-54). Presence of abnormally high activities of the pancreatic isoamylase in serum corresponding to acute pancreatitis was seen in all groups. However, the prevalence of acute pancreatitis was not seen to increase progressively with duration of alcoholism. By studying the decrease of pancreatic isoamylase a rebound effect with elevated serum amylase activity was often seen during the abstinent period in patients with initially low pancreatic isoamylase. Explanations for this finding may be several. One explanation could be suppression due to toxic effect of ethanol on the exocrine pancreas (55). Another explanation may be deficient nutrition during the debauch (56) as in patients with severe malnutrition have been observed to have a reduced pancreatic isoamylase activity (57). It is also known that pancreatic dysfunction may occur in protein calorie malnutrition (58, 59). In this patients, however, there is no positive correlation between the albumin concentration and pancreatic isoamylase activity in serum at admission, lending little support to the theory of malnutrition. The theory of toxic suppression seems more probable in view of the rebound phenomenon observed during abstinence.

Elevation of pancreatic isoamylase in the healthy pancreas, after ERCP disappears within 5 days (60). The longer duration and rebound phenomenon among alcoholics indicate that ethanol behaves as something other than a simple chemical irritant in a healthy pancreas. The lack of correlation between S-GT, S-ASAT and pancreatic isoamylase activities suggests that this analysis is a useful complement to the hepatic analyses in detection of alcoholics.

Among 18 patients where serum pancreatic isoamylase activity was determined prior to ERCP, 4 patients were found to have normal isoamylase activities with ERCP verified signs of pancreatitis. Although the specific toxic effect of ethanol on the pancreas is unclear a rather high frequency of both pathological pancreatic isoamylase activities and morphological changes in the pancreas are seen in cases of alcoholism with a duration more than 5 years.

Many authors have reported hypokalemia in chronic alcoholics (61-68). It is obvious that the total body potassium is markedly reduced in many alcoholic patients. The depletion of potassium has primarily been explained by deficient nutrition and gastro-intestinal losses during intoxication. The low values during severe ethanol withdrawal have also been explained by respiratory alkalosis (65, 69) which causes a shift of potassium into cells. In this study serum potassium was continuously followed in chronic alcoholics. All these patients had normal serum potassium levels at admission but shortly before and during DT, the patients showed a transient hypokalemia. The decrease of serum potassium could not be attributed to urinary or gastrointestinal losses. A rapid shift of potassium into the intracellular compartment is postulated. The mechanism is still obscure, but one hypothesis is that ethanol inhibits Na-K-ATPase leading to an increase of the intracellular Na-K-ratio. This derangement of electrolyte balance is counteracted during ethanol withdrawal by increased levels of epinephrine and nor-epinephrine and may stimulate Na-K-ATPase in striated muscle, heart muscle and brain, possibly leading to hyperpolarization of these cells and to hypokalemia during delirium tremens (70, 71).

Even if the pathophysiology is not known in detail the observation of serum potassium levels may be used to predict DT and as a help in the diagnosis of DT in neurologically unclear patients. The combination of a long history of alcoholism with a current debauch of long duration and the observation of mental confusion with falling serum potassium is highly indicative of DT. This is especially valuable in the differential diagnoses of other psychic disorders. Determination of serum potassium may also be used to decide when the patients are ready for ambulatory treatment. As long as there is a risk for DT patients should be hospitalized. Excessive intravenous fluid therapy and potassium substitution should be avoided in cases of DT, if there is no other reason for hypokalemia as i.g. cirrhosis or excessive gastro-intestinal losses. In such cases, of course, an adequate substitution is necessary, which is in agreement with other authors (72).

Serum potassium is valuable as a predictor for DT and not, of course, as a screening test for alcoholism in general.

Changes in all biochemical parameters discussed above have been seen among hospitalized chronic male alcoholics. Voluntary hospitalization presents an unavoidable bias in the population studied, the significance of which is uncertain concerning alcoholism in general.

New markers

Using the above described biochemical markers nearly all cases of alcoholism can be detected. The toxic effects of ethanol are many and give somatic manifestations in nearly all organs of the body. Even chromosomal damages are reported at ethanol concentrations exceeding 90 mmol/l (4.14 mg/ml) (73). New markers for detecting and following specific somatic effects are both desirable and necessary. The presented markers are connected with damage to liver or pancreas, but other more indirect markers could also be of great value. One of those, e.g. HDL is discussed. We have recently investigated the potential marker S-Ferritin (74), which is elevated in hemochromatosis, malignancy, cirrhosis of the liver, acute hepatitis (75), infections (76) and heavy alcohol consumption (74). Patients with shorter debauches than 5 days had neither elevated S-GT nor elevated S-Ferritin values. Those with debauches more lengthy than 5 days had a higher frequency of elevated S-Ferritin values than S-GT values. This pattern remained for a period up to 8 weeks of daily ethanol intake. With a debauch of more than 8 weeks the S-Ferritin values and S-GT values were elevated in the same frequency. In our opinion this seems to be a good early diagnostic tool. Another useful marker could be P-antithrombin III, which recently has been shown to be pathological in 40 per cent of chronic alcoholics on admission to hospital (77). 20 per cent of the patients had pathologically low values of P-antithrombin III and 21 per cent elevated above the upper reference limit, perhaps explaining the predisposition of alcoholics for thrombosis and hemorrhage, respectively (77). IgA is frequently markedly elevated in alcoholics (34) but the physiological significance of this observation is unclear. Other serum proteins which could be used are e.g. plasma alpha-1-antichymotrypsin, which is elevated in about 60 per cent of chronic alcoholics on admission to hospital (78). Plasma prealbumin is also elevated (78) just as plasma orosomucoids (78), which have been shown to correlate to degree of hepatic steatosis (79).

Analysis of U-GT shows a significant elevation during ethanol abstinence (80). During long-standing consumption there is an adaption to U-GT levels, which do not differ from a healthy reference population of the same age. In intoxications with isopropyl alcohol, which has become common in Sweden

among advanced alcoholics, acetonuria is a constant and reliable finding independent of serum acetone or isopropyl alcohol levels (81), as well as significantly elevated U-GT. (81).

How should different markers be used?

These markers may be used in several different ways.

1. As a screening procedure for hidden alcoholism.
2. In cases of known alcoholism for control of treatment and detection of new debauches.
3. As motivation for sobriety in the informed patients, laboratory values may function as rapid biological feedback.
4. For colleagues, who in their daily work, do not treat alcoholics or primarily alcohol induced disorders, the laboratory diagnosis in disorders such as gastritis, ulcer, unclear abdominal pain, trauma, fractures and hypertonia, may suggest the correlation with advanced consumption of ethanol.

The pattern of elevated values among several markers in combination may lead to more specific diagnosis of particular somatic disorders. It is hoped that by early detection, patient information and motivation, total alcohol consumption may be reduced and development of advanced alcoholism may be diminished.

Summary

Investigated were 396 alcoholic patients. In 182 patients at admission to hospital values of S-bilirubin, S-ASAT, S-ALAT, S-GT were analyzed. In 156 patients the decrease of S-ASAT, S-ALAT, S-GT was followed over 9 days in the abstinence phase. In another 40 patients the interrelationships between serum ethanol, S-ASAT, S-ALAT, S-GT and length of debauch were analyzed. In 36 patients plasmalipoprotein was analyzed. By zonal ultra centrifugation subclasses of HDL could be determined. In 18 patients ERCP was performed. The relationship between changes in pancreas- and isoamylase pattern in these patients as discussed. Potassium was followed in 37 patients from admission and during delirium tremens which developed in 26 of the patients.

S-GT as well as S-ASAT were elevated in 69 and 73 per cent respectively at admission to hospital. S-ALAT was elevated in 53 per cent. During abstinence there was a decrease in these "hepatic enzymes" with a normalization of S-ASAT and S-ALAT for those patients with only moderately elevated values. The GT decrease was slower and after 9 days there remains an elevation in most of the patients. One factor affecting the elevation of the hepatic enzymes could be length of debauch. Patients with a long history of alcoholism achieve the highest levels of ethanol, but also had the shortest length of debauch.

HDL was changed in the subclasses in all the 8 patients investigated with zonal ultra centrifugation. HDL seemed in combination with the other parameters to be valuable in detecting alcoholism.

The pancreas was affected in patients with a long history of alcoholism which was demonstrated both by help of isoamylase studies and ERCP. In patients with more than 5 years of alcoholism there was a high incidence of both morphological changes in the pancreas and pathological isoamylase pattern.

S-potassium seemed to decrease just before and during delirium tremens. After the DT episode there was a rapid normalization of S-potassium. S-potassium seemed to be a good predictor and a useful aid in differential diagnoses in patients with possible delirium tremens.

Acknowledgements

My sincere thanks are due to
Barbro Lanke, M.D., Head of the Department of Alcohol
Diseases, Malmö Genereal Hospital, Sweden, for her great
interest and constant support during the study,
Åke Nordén, Professor of Medicine, University Hospital,
Lund for helpful guidance,
Bertil Hood, Anders Gustafson, Professors at the Medi-
cal Clinics, Malmö General Hospital and the University
Hospital, Lund and Carl-Bertil Laurell, Professor of
Clinical Chemistry, Malmö General Hospital for construc-
tive criticism,
my co-authors especially Gunnar Skude, Dept. of the Cli-
nical Chemistry, Central Hospital, Kalmar, Sweden, for
excellent co-operation during last decade,
Bengt Danielson, Göran Fex, Bengt G. Johansson, Peter
Nilsson-Ehle and Hans Kristenson for pleasant and re-
warding collaboration,
Joyce Carlson, M.D. for excellent help with translation
and discussion,
colleagues and co-workers at the Clinic of Alcohol Di-
seases for all valuable help in collecting the materials
and fruitful discussions,
secretarial help for typing and retyping I am very gra-
teful to Gertrude, Inger-Lis, Lena, Lise-Lotte, Synnöve
and Ulla.
Investigation IV was supported by grants from the
Swedish Medical Research Council (03X-4147, 03X3364)
and the Medical Faculty, University of Lund.

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